

WHAT IS CLAIMED IS:

1. A method for identifying an agent that modulates HFE2A gene expression, comprising:
  - 5 (a) contacting a test compound with a genetic construct comprising a reporter gene operably linked to an HFE2A promoter under conditions supporting expression of said reporter gene;
  - (b) determining a change in expression of said reporter gene as a result of said contacting,
- 10 wherein a change in expression identifies said test compound as an agent that modulates HFE2A gene expression.
2. The method of claim 1 wherein said modulation is an increase in expression of said reporter gene.
3. The method of claim 1 wherein said modulation is a decrease in
- 15 expression of said reporter gene.
4. The method of claim 1 wherein said HFE2A promoter is a mammalian HFE2A promoter.
5. The method of claim 4 wherein said mammal is a member selected from the group consisting of mouse, rat and human.
- 20 6. The method of claim 1 wherein said promoter has the nucleotide sequence of SEQ ID NO: 19.
7. The method of claim 1 wherein said genetic construct is in a cell.
8. The method of claim 7 wherein said cell is a mammalian cell.
9. The method of claim 7 wherein said cell is a recombinant cell
- 25 engineered to express said gene and wherein said cell does not express said gene absent said engineering.
10. The method of claim 8 wherein said mammalian cell is a macrophage, inflammatory cell, liver cell, hepatocyte, intestinal cell, hematopoietic cell, pancreatic cell, skeletal muscle cell or a nervous system
- 30 cell.

11. The method of claim 1 wherein said test compound is useful in controlling iron metabolism.

12. The method of claim 1 wherein said test compound is first identified as an agent that modulates HFE2A gene expression using said method.

5 13. The method of claim 1 wherein said change is determined by measuring a change in an enzyme activity.

14. A method for identifying an agent that modulates HFE2A gene expression, comprising:

10 a) contacting a test compound with a cell expressing an HFE2A gene;  
b) determining a change in expression of said HFE2A gene as a result of said contacting,

wherein a change in expression identifies said test compound as an agent that modulates HFE2A gene expression.

15 15. A method for identifying an agent that modulates the activity of an HFE2A polypeptide, comprising:

a) contacting a test compound with an HFE2A polypeptide under conditions supporting an activity of said polypeptide; and

b) determining a change in said activity of said polypeptide as a result of said contacting,

20 wherein a change in the activity identifies said test compound as an agent that modulates the activity of an HFE2A polypeptide.

16. The method of claim 15 wherein said HFE2A polypeptide is a mammalian HFE2A polypeptide.

25 17. The method of claim 16 wherein said mammal is a member selected from the group consisting of mouse, rat and human.

18. The method of claim 15 wherein said change is a decrease in said activity.

19. The method of claim 15 wherein said change is an increase in said activity.

30 20. The method of claim 15 wherein said polypeptide is part of a cell.

21. The method of claim 20 wherein said cell is a mammalian cell.

22. The method of claim 20 wherein said cell has been engineered to contain said polypeptide.

23. The method of claim 22 wherein said cell was engineered by genetic engineering.

5        24. The method of claim 23 wherein said cell does not contain said polypeptide absent said engineering.

25. The method of claim 20 wherein said cell is a macrophage, inflammatory cell, liver cell, hepatocyte, intestinal cell, hematopoietic cell, pancreatic cell, skeletal muscle cell or a cell of the nervous system.

10       26. The method of claim 15 wherein said HFE2A polypeptide is highly purified.

27. The method of claim 15 wherein said HFE2A polypeptide is a semi-purified polypeptide.

15       28. The method of claim 15 wherein said HFE2A polypeptide is attached to a solid surface.

29. The method of claim 28 wherein said solid surface is a resin.

30. The method of claim 15 wherein said HFE2A polypeptide is part of an extract.

20       31. The method of claim 15 wherein said polypeptide is encoded by a polynucleotide having the sequence selected from the group consisting of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8 and 9.

32. The method of claim 15 wherein said polypeptide comprises an amino acid sequence selected from SEQ ID NO: 10, 11 and 12.

25       33. A method for treating a disorder comprising administering to an animal afflicted therewith a therapeutically effective amount of an HFE2A modulator.

34. The method of claim 33 wherein said HFE2A modulator exhibits modulating activity in a method of claim 1, 14 or 15.

30       35. The method of claim 34 wherein said modulator was first identified as an HFE2A modulator using said method.

36. The method of claim 33 wherein said HFE2A modulator is a member selected from the group consisting of a selective HFE2A agonist, a selective HFE2A antagonist, pharmaceutically acceptable salts thereof, and combinations of these.

5        37. The method of claim 36 wherein said member is in a pharmaceutically acceptable carrier.

38. The method of claim 33 wherein said HFE2A modulator is selected from an antibody, an anti-sense molecule, a ribozyme and a drug-like small organic molecule.

10       39. The method of claim 33 wherein said disorder is a disease of iron metabolism.

40. The method of claim 39 wherein said disease of iron metabolism is a member selected from the group consisting of an iron overload disorder and an iron deficiency disorder.

15       41. The method of claim 39 wherein said disease of iron metabolism is a member selected from the group consisting of hemochromatosis, transfusion iron overload, thalassemia, porphyria, and juvenile hemochromatosis.

20       42. The method of claim 39 wherein said disease of iron metabolism is a member selected from the group consisting of anemia and anemia of chronic disease.

43. The method of claim 39 wherein said disease of iron metabolism is a member selected from Type I diabetes, Type II diabetes and insulin resistance.

25       44. A method for preventing a disorder comprising administering to an animal, at risk of developing said disorder, a therapeutically effective amount of an HFE2A modulator.

45. The method of claim 44 wherein said HFE2A modulator exhibits modulating activity in a method of claim 1, 14 or 15.

30       46. The method of claim 45 wherein said modulator was first identified as an HFE2A modulator using said method.

47. The method of claim 44 wherein said HFE2A modulator is a member selected from the group consisting of a selective HFE2A agonist, a selective HFE2A antagonist, pharmaceutically acceptable salts thereof, and combinations of these.

5        48. The method of claim 47 wherein said member is in a pharmaceutically acceptable carrier.

49. The method of claim 44 wherein said HFE2A modulator is selected from an antibody, an anti-sense molecule, a ribozyme and a drug-like small organic molecule.

10       50. The method of claim 44 wherein said disorder is a disease of iron metabolism.

51. The method of claim 50 wherein said disease of iron metabolism is a member selected from the group consisting of an iron overload disorder and an iron deficiency disorder.

15       52. The method of claim 50 wherein said disease of iron metabolism is a member selected from the group consisting of hemochromatosis, transfusion iron overload, thalassemia, porphyria, and juvenile hemochromatosis.

20       53. The method of claim 50 wherein said disease of iron metabolism is a member selected from the group consisting of anemia and anemia of chronic disease.

54. The method of claim 50 wherein said disease of iron metabolism is a member selected from Type I diabetes, Type II diabetes and insulin resistance.

25       55. A method to diagnose individuals affected by or at risk of developing a disease of iron metabolism comprising determining a mutation or polymorphism in the nucleic acid sequence of the HFE2A gene in said individual wherein said mutation or polymorphism in said gene identifies said individual as being affected by or at risk of developing a disease of iron  
30       metabolism.

56. The method of claim 55 wherein said mutation or polymorphism is a mutation or polymorphism of Table 1.

57. A method to diagnose individuals affected by or at risk of developing a disease of iron metabolism comprising determining a mutation or polymorphism in the amino acid sequence of HFE2A polypeptide in said individual wherein a mutation or polymorphism of said HFE2A polypeptide identifies said individual as being affected by or at risk of developing a disease of iron metabolism.

58. A method to diagnose individuals affected by or at risk of developing a disease of iron metabolism comprising determining a decrease in level or amount of an HFE2A polypeptide in said individual wherein said decrease identifies said individual as being affected by or at risk of developing a disease of iron metabolism.

59. The method of claim 55, 56, 57 or 58 wherein said disease of iron metabolism is adult onset hemochromatosis.

60. The method of claim 55, 56, 57 or 58 wherein said disease of iron metabolism is juvenile hemochromatosis.

61. The method of claim 55, 56, 57 or 58 wherein said disease of iron metabolism is selected from Type I diabetes, Type II diabetes and insulin resistance.

62. A method for identifying a compound capable of modulating a HFE2A activity, comprising: (a) contacting a test compound with a cell that expresses HFE2A; and (b) assaying the ability of said test compound to modulate the transcription of a HFE2A nucleic acid or the activity of HFE2A polypeptide, thereby identifying a compound capable of modulating a HFE2A activity.

63. The method of claim 62, wherein the compound is an anti-HFE2A polypeptide antibody.

64. The method of claim 62, wherein the compound is an antisense HFE2A nucleic acid molecule.

65. The method of claim 62, wherein the compound is a HFE2A ribozyme.

66. The method of claim 62, wherein the compound is a small organic molecule.

5        67. An isolated polynucleotide comprising a polynucleotide having a nucleotide sequence with at least 60 percent identity to a sequence selected from the group consisting of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 19, 20, 21 and 22.

10       68. The isolated polynucleotide of claim 67 wherein said percent identity is at least 70 percent.

69. The isolated polynucleotide of claim 67 wherein said percent identity is at least 78 percent.

70. The isolated polynucleotide of claim 67 wherein said percent identity is at least 90 percent.

15       71. The isolated polynucleotide of claim 67 wherein said percent identity is at least 95 percent.

72. The isolated polynucleotide of claim 67 wherein said percent identity is at least 98 percent.

20       73. The isolated polynucleotide of claim 67 wherein said nucleotide sequence is a member selected from the group consisting of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 19, 20, 21 and 22.

25       74. An isolated polypeptide comprising a polypeptide having an amino acid sequence with at least 90 percent identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 11, 12, 23, 24, 25, 26, 27 and 28.

75. The isolated polypeptide of claim 74 wherein said percent identity is at least 95 percent.

76. The isolated polypeptide of claim 74 wherein said percent identity is at least 98 percent.

30       77. The isolated polypeptide of claim 74 wherein said amino acid sequence is selected from the group consisting of SEQ ID NO: 10, 11, 12, 23, 24, 25, 26, 27 and 28.

78. A cell line comprising a recombinant form of the polynucleotide of claim 67.

5 79. A cell line comprising a recombinant form of the polypeptide of claim 74.

80. Use of a cell line of claim 78 or 79 in a method for identifying compositions which modulate expression or activity of hemojuvelin.

10 81. A composition for treating a disease of iron metabolism comprising a therapeutically effective amount of a polypeptide of claim 74 in a pharmaceutically acceptable carrier.

82. A method for treating a disease of iron metabolism comprising administering to a patient in need thereof a therapeutically effective amount of a composition of claim 81 in a pharmaceutically acceptable carrier

15 83. The method according to claim 82, wherein said disease is juvenile hemochromatosis.

84. A method for producing test data with respect to the modulation of HFE2A gene expression by a compound, comprising:

20 (a) a genetic construct comprising a reporter gene operably linked to an HFE2A promoter under conditions supporting expression of said reporter gene;

(b) determining a change in expression of said reporter gene as a result of said contacting, wherein said change shows modulation, and

25 (c) producing test data with respect to the gene modulating activity of said test compound based on a change in expression of the determined genes indicating gene modulating activity.

85. A method for producing test data with respect to the modulation of an HFE2A polypeptide activity by a compound, comprising:

(a) contacting a test compound with an HFE2A polypeptide under conditions promoting an activity of said HFE2A polypeptide;

30 (b) determining a change in activity of said polypeptide as a result of said contacting, wherein said change shows modulation, and



(c) producing test data with respect to the HFE2A polypeptide modulating activity of said test compound based on a change in an HFE2A polypeptide activity indicating modulating activity.

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